UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/709,801	05/28/2004	Caroline Desponts	USF-212XZIT	2999

23557 7590 09/22/2008

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/709,801	DESPONTS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18-20,22 and 24-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 18-20, 22, and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-14-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 8-14-08.

Claims 1, 18-20, 22, and 24-34 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-14-08 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-32, 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro reduction of expression of SHIP-1 in embryonic stem cells, and being enabling for the in vivo inhibition of SHIP expression in peripheral blood mononuclear cells, thereby increasing Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells), and in hematopoietic cells using siRNA, does not reasonably provide enablement for methods of increasing the yield of embryonic stem cells in a patient for the reasons of record set forth in the Office action mailed 11-14-07.

Applicant's arguments filed 8-14-08 have been fully considered but they are not fully persuasive. Applicant argues that the full scope is enabled, including the ability to increase the number of embryonic stem cells in a subject, because the Applicant teaches that the hematopoietic stem cell population is increased significantly in SHIP-deficient mice and so this would be expected if SHIP expression were inhibited by another means, *e.g.* via siRNA. Applicant also argues that in vivo SHIP inhibition by siRNA has provided an increase in SHIP-expressing cells, *e.g.*, hematopoietic stem cells in test animals. Applicant teaches partial inhibition of expression of SHIP-1 in vivo using siRNA (*a.k.a.* RNAi). Applicant argues that the inhibition of expression of SHIP in embryonic stem (ES) cells transfected in vitro has been demonstrated using siRNA. Applicant also argues that the in vivo inhibition of SHIP expression has been shown in peripheral blood mononuclear cells, with a concomitant increase in Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells) following RNAi inhibition of SHIP-1 in vivo.

The claims, however, are broadly drawn to methods of increasing the yield of embryonic stem cells in a patient, which methods comprise administration of an RNAi compound that inhibits SHIP expression in a patient, and which methods optionally further comprise subsequently harvesting stem cells from the patient, and optionally re-administering the harvested stem cells to the patient.

Contrary to Applicant's assertions, the examples delineated above regarding the inhibition of SHIP in vitro and in vivo do not enable the full scope of the claimed invention. Applicants have not provided guidance in the specification toward a method of increasing the number of embryonic stem cells in vivo comprising the administration of an RNAi specific for SHIP mRNA. Applicant has shown the inhibition of expression of SHIP in embryonic stem (ES) cells transfected in vitro using siRNA. Applicant has shown the in vivo inhibition of SHIP expression in peripheral blood mononuclear cells, thereby increasing Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells) using siRNA. The ability to inhibit SHIP-1 expression in ES cells in vitro and to inhibit SHIP-1 expression in vivo using siRNA, whereby Mac+Gr1-monocytes and circulating Mac1+GR1+ cells are increased in vivo, are not representative or correlative of the ability to increase the yield of any and/or all embryonic stem cell types in an organism, including but not limited to mammary stem cells, mesenchymal and organ specific stem cells in a patient.

One skilled in the art would not accept on its face the examples given in the specification of in vitro transfections, of biochemical, cellular and immunological characterization of stem and other progenitor cells obtained from mouse ablation

models, and increasing Mac+Gr1-monocytes and circulating Mac1+GR1+ cells in vivo following SHIP-1 inhibition using siRNA as being correlative or representative of the ability to increase the yield embryonic stem cells in a subject. This is in view of the lack of guidance in the specification and known unpredictability associated with the ability to deliver nucleic acids to embryonic stem cells in vivo, whereby their numbers are increased.

The unpredictability of embryonic stem cell transfection, expansion and stem cell fate in vitro and in vivo is well known in the art and has been discussed in numerous references. See for instance Odorico et al, Cell, Vol. 88, pages 13-17, 1997; Hemmati-Vrivanlou et al, Cell, Vol. 88, pages 13-17, 1997; and Zwaka et al, Nature Biotech., online publication on Feb. 10, 2003: doi: 10.1038/nbt788..

The breadth of the claims is broad. The claims are drawn to methods of increasing the yield of embryonic stem cells in a patient, which methods comprise the administration of any RNAi compound that inhibits SHIP expression in a patient, and which methods optionally further include harvesting stem cells from the patient, and optionally re-administering the harvested stem cells to the patient.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target embryonic stem cells and harboring the target gene or genes SHIP, whereby SHIP expression is effectively inhibited in embryonic stems cells in vivo, and further whereby the number of embryonic stem cells is predictably increased in a subject following administration of any RNAi that targets SHIP. Since the specification

fails to provide any particular guidance for the successful increase in embryonic stem cells in a patient comprising administration of an RNAi, and since determination of the factors to effectively transfect and subsequently increase embryonic stem cells claimed in a patient is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1, 18-20, 22, 24-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38-44, 74-76, 90, 94 of copending Application No. 09/955,174 in view of Fire et al (USPN 6,506,559) and Patchen et al (USPN 6,117,850) insofar as the claims are drawn to methods of

increasing the number of hematopoietic stem cells in a subject comprising the administration of RNAi which specifically targets and inhibits the expression of SHIP, and further comprising harvesting the transfected stem cells using leukopheresis.

This is a provisional obviousness-type double patenting rejection.

Copending Application No. 09/955,174, claims 38-44, 74-76, 90, 94, claims methods for reducing SHIP-1 function in hematopoiteic cells comprising administering an efficacious amount of RNA specific for SHIP-1 mRNA present in hematopoietic cells. Copending Application No. 09/955,174 does not explicitly disclose the use of RNAi molecules for inhibiting the target SHIP gene.

Fire et al (USPN 6,506,559) teach the use of RNAi molecules in targeting and inhibiting the expression of target genes of known sequence. Fire also teaches the advantages of using RNAi molecules for target gene inhibition compared to other inhibitory oligonucleotides, including antisense and ribozymes (see esp. col. 1-7, claims 1-3).

Patchen et al (USPN 6,117,850) teach the routine use of leukophoresis for isolating and harvesting transfected cell populations from a patient (see esp. example 8).

It would have been obvious to combine the teachings of Fire and Patchen to render the instant claims obvious in view of claims 38-44, 74-76, 90, 94 of the copending Application No. 09/955,174 because RNAi were well known in the art to provide inhibition of known target genes as instantly claimed, and the use of leukophoresis to harvest transfected cells in a subject were well known in the art, as

taught previously by Patchen et al. One of ordinary skill in the art would have been motivated to use RNAi molecules for target gene inhibition because RNAi molecules were well known to provide increased inhibition compared to other inhibitory oligonucleotides, as taught previously by Fire. One of ordinary skill in the art would have reasonably expected that the RNAi inhibition would provide for effective SHIP inhibition and leukophoresis would provide for harvesting of the transfected hematopoietic cells from a patient.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of

a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
9-17-08

/Jane Zara/

Primary Examiner, Art Unit 1635